

The Development, Implementation and Evaluation  
of Three Instructional Units for an  
Honors Symposium in Human Genetics

An Honors Thesis (ID 499)

by

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A handwritten signature in cursive script that reads "Thomas R. Mertens".

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## *PREFACE*

This thesis is the product of nine months of diligent work. It describes the process by which new material was developed, implemented, and evaluated for possible incorporation into a college course on human genetics. This process, by itself, is very common. The uniqueness of this study derives from the fact that it was conducted by a student who, only two years earlier, had filled one of the seats in the class in which the material was presented.

It was with great pleasure that I accepted the opportunity to experience first-hand the process of developing instructional material. I enjoyed immensely the opportunity to read extensively in the field of human genetics and to participate in Biology 199. In addition, I gained an appreciation of the caring and dedication required of educators who strive to provide significant learning experiences for their students.

I am indebted to Dr. Thomas R. Mertens, my thesis director, who provided not only the idea, but also the inspiration for this project. He spent numerous hours editing rough drafts, reading final copies and providing motivation in my less than diligent moments. Dr. Mertens is the epitome of kindness, concern and consideration.

Dr. Jon R. Hendrix, as well, receives my gratitude. He graciously gave several hours of his valuable time to read and respond to the material I developed. He opened his Biology 199 class to my project, allowing me to present and to test the material I had developed.

Several other individuals deserve my gratitude. Dr. Nancy Behforouz contributed her expertise in the areas of virology, immunology, and oncology to assist in the development of the unit on the molecular basis of cancer. Karen Vincent typed with skill and good humor more essays than I had a right to ask her to type. Debbie Bowen, who taught the human genetics component of Biology 199, not only allowed me the time I requested for presenting my material, but also convinced some occasionally less-than-willing students to volunteer for my research.

The students who enrolled in Biology 199 during the 1986–1987 academic year and who participated in my research also receive my appreciation.

Without the help and support of the people I have listed, this thesis would not have been possible. It is with that knowledge that I extend my heartfelt thanks.

## INTRODUCTION

In today's rapidly changing world, new knowledge is produced at an extraordinary rate. Often new theories are generated, updated and discarded even before they have been widely disseminated. In no field is this process more true than in the biological sciences. Phenomenal advances with far-reaching implications have catapulted science and scientists into the limelight. Technological advances have the power to influence world events and to direct the course of history (Kieffer 1979).

One topic in the field of biology — human genetics — has commanded special interest (Mertens 1983). Human genetics involves the branch of biology that deals with heredity and variation as it applies to members of the species Homo sapiens. In the past thirty years, gigantic strides in this area have solved many mysteries and uncovered thousands more. Equipped with site-specific DNA splicing enzymes, radioactively labelled DNA probes, and automated DNA sequencers, researchers are rapidly closing in on even the most elusive secrets of the human genome. Approximately 3,000 human genetic diseases and defects have been identified. Every year another one hundred or more diseases and defects are added to the list (Mertens 1983).

It is said that the doubling time for new scientific information in the field of human genetics is two years (Mertens and Hendrix 1983). This means that two years ago there was only one-half as much information about human genetics as there is today and that two years from now there will be twice as much information as there is today. Modern society is truly living in an "information explosion" (Combs 1981). Combs (1981) states that "ninety percent of all the scientists who ever lived are alive today." They produce over 100,000 different technical journals today and will produce another 100,000 by the twenty-first century. The

predictions of W.C. Miller (1978) have come true. The rate of social and technological change is accelerating and the indications are that it will continue even faster in the future (Miller 1978).

Faced with this deluge of information, it is often difficult for researchers, let alone lay people, to keep up with the ever-expanding volumes of knowledge. Members of the scientific community charged with the responsibility of passing on the accumulated volumes of knowledge find it particularly frustrating. In addition to teaching the basic principles and concepts of human genetics, educators are bound by an obligation to themselves and their students to provide up-to-date, accurate information. Educators, by their position, must be aware of the needs, problems, and interests of the society which they serve (Yager *et al.* 1981). They are responsible for not only relating the facts, but also for interpreting the influence of technology on society. Educators must choose almost daily what topics to stress in a field where one breakthrough can change overnight an obscure bit of trivia into a prominent find with significant social, economic and ethical implications.

It is no longer possible for educators to provide solely factual information for their students. With the development of television, radio and computers, a large amount of information is readily available to most people (Combs 1981). It is neither possible nor desirable for the individual to master all the information with which he or she comes in contact. Miller (1978) estimates that eighty percent of all "learned" information is forgotten within six months. There is no need for teachers to add to these volumes of forgotten material. If the primary goal of education has always been "preparation for the future" (Combs 1981), then society's technological future does not demand a review of facts, but rather a comprehensive curriculum

that integrates both society and science.

In contemporary society it is no longer possible to ignore on a personal or societal level the technological changes that have taken place. Basic research, once the foundation of science, has been almost completely replaced by applied research (Hoskins 1979). The slow development and application of basic research provided a "safety net" which allowed scientists and society at large an opportunity to evaluate a pending program before it was implemented. With the shift to applied research, a new technology may be put into practice before its consequences can be fully appreciated by either the scientists who created it or the society which must live with it.

The new goal of science education ought to be to develop knowledgeable, scientifically literate individuals (Combs 1981). Many observers believe that the public's scientific literacy is currently too low to combat the pressing problems created by advances in technology (Prewitt 1982). The world is in desperate need of educated citizens who are capable of making informed decisions about the way society applies its technological developments. Through education, society must establish an "attentive public" which concerns itself with both the scientific and societal implications of such developments as recombinant DNA research, genetic screening programs, and prenatal diagnosis techniques (Prewitt 1982). In promoting scientific literacy, society would be encouraging more knowledgeable consumers, better producers, and an improved future for all mankind (Thellen 1983; Lucas 1981).

If society is to develop an effective citizenry, science education requires change. In teaching science, emphasis must no longer be placed on just accumulating facts. Education ought to be expanded to include instruction in communication, critical thinking and decision-making skills as well as important biological principles so that future problems will not be left unsolved

simply because students were never confronted with similar problems in their schoolwork (Yager *et al.* 1981). Process skills such as observing, questioning, hypothesizing, analysing, and inferring must be developed so that students can begin to understand the advantages and disadvantages of scientific progress in order to make better decisions. Flexibility and creativity must be encouraged so that pupils will look beyond short-term solutions and explore long-range possibilities in an attempt to solve the most pressing problems of society.

In addition, moral, ethical, and value development ought to be given consideration in science education (Miller 1978). In the face of cultural plurism and world-wide interdependence, the values expressed in science must be constantly reevaluated. Biological knowledge (and, in particular, human genetics knowledge) is most effective when presented "in conjunction with the social, legal, economic, moral, ethical and religious/theological issues raised by these developments" (Mertens 1983). Students must be taught how to decide what is "right" on both a personal and societal level. By implementing an educational program that stresses individualized critical thinking along with the biological facts necessary to make a decision, the individual may learn to deal with the ambiguity inherent in many of the situations created by the rapid advances of technology (Romanish 1986).

Members of society must have some understanding of the significance of the new biological technologies if they are to make intelligent decisions about their welfare and the welfare of future generations (Yager *et al.* 1981). Technological advances have made members of society increasingly interdependent (Combs 1981). One individual with less than humanitarian motives may develop, with present technologies, the power to destroy society, a power already held by many of the world's governments. In making life easier and more productive,



technology has brought with it additional responsibilities which require individuals to consider carefully the consequences of their choices and how they may affect others (Keiffer 1979).

Realizing the validity of this situation, it was suggested that an attempt be made to explore some of the areas within the field of human genetics exhibiting critical advancements for possible incorporation into a college course in basic human genetics. Not only was it necessary to select biologically significant topics from the volumes of literature available, but it was also necessary to choose topics which show some relevance to the student's life. Many students come to college with unfavorable attitudes towards science (Mertens and Hendrix 1983). They often see little relevance to the "meaningless facts" spewed forth by the educator, swallowed by the student, and regurgitated on tests (Yager and Penick 1984). As Chen and Novik (1984) note "We cannot sustain a curricula [sic] detached from man's everyday ordinary experiences.... No part is meaningful unless it is understood in relation to the whole." Research suggests that students perform best when they confront real, personally relevant problems for which solutions within their capabilities are possible and visible. By selecting topics directly applicable to the student's life, it may be possible to motivate even the nonscience major to obtain the degree of scientific literacy needed to cope with the scientific and technological world of today.

The intent of this investigation was to identify topics in human genetics of interest to students and to provide instruction on these topics in an attempt to increase their scientific literacy. Three topics — the molecular basis of cancer, human gene therapy, and prenatal diagnosis — were chosen for research. The information was incorporated into instructional objectives, short essays, and visual aids for presentation to the student. The instructional

materials were then evaluated for their effectiveness as teaching tools.

## *PROCEDURE*

### **DESIGN**

The investigations conducted in this study used two pre-experimental research designs to estimate the effectiveness of the materials as teaching tools. A post-test only format was used in the evaluation of the unit on prenatal diagnosis, while a one-group pretest/ post-test format was used to evaluate the effectiveness of the units on the molecular basis of cancer and human gene therapy.

Each pretest or post-test consisted of twenty multiple choice questions. The tests were designed to evaluate the instructional objectives issued to the students at the beginning of each unit. Post-tests consisted of the same questions posed in the pretests, but reordered to lessen any effects that may have resulted from the student having been previously exposed to the test material.

In addition, students were asked to complete, anonymously, descriptive evaluations in order to provide information for possible revision of the materials.

### **SAMPLE**

Forty-eight Honors College students enrolled in Biology 199 at Ball State University in Muncie, Indiana, during the spring quarter of the 1986- 1987 academic year participated in the evaluation of all of the instructional material ( the molecular basis of cancer , human gene therapy, and prenatal diagnosis). All students were taking Biology 199 for the first time. Class participation in the research exercises ranged from sixty-nine to one hundred percent. Sixty-two percent of the students had had some prior instruction in genetics. Only two percent of the students had received instruction in bioethics. Because Biology 199 is required for all Honors College students, a variety of different majors ranging from architecture to education to

psychology was represented; however, no biology majors were present in the sample.

The sample used in this investigation is typical of Biology 199 classes. Students for the class were chosen by computer, based upon the number of credit hours completed, as is the normal university policy. Although it is open to all Honors College students, the majority of students choose to complete this requirement in their freshman year.

Materials were also presented to students enrolled in the same class during both the fall and winter quarters of the 1986–1987 academic year. The enrollment for these two classes combined was approximately 150 students. These students were chosen for the class as described above. Information obtained from the fall quarter students was used to revise the material on the molecular basis of cancer, while the information obtained during the winter quarter was used to revise the material on human gene therapy.

## **CLASS STRUCTURE**

Biology 199 — Honors Symposium in Biology: Human Genetics and Bioethical Decision Making — is a unique course required for all students graduating from the Ball State University Honors College. The goal of this symposium, as described by Mertens and Hendrix (1983), is two-fold. The first objective of the course is to provide basic instruction in human and medical genetics in an attempt to increase genetic literacy. The second goal is, through lectures and prepared bioethical decision-making strategies, to help students to "clarify their values and formulate personal decisions on the controversial issues that arise from the application of new genetic knowledge and technologies" (Hendrix *et al.* 1983). Four fifty-minute class sessions

are conducted each week. Approximately two class periods per week are devoted to the study of basic principles and concepts of human genetics. One lecture per week revolves around the presentation of a bioethical issue. The remaining class period is reserved for small group discussions, laboratory exercises, and quizzes. Class notes, diagrams, instructional objectives and supplementary readings are usually distributed in mimeographed form the week prior to their discussion.

## **MATERIALS**

Research of the chosen topics — the molecular basis of cancer, human gene therapy, and prenatal diagnosis — began in early September of 1986. Scientific journals and scientifically-sound popular magazines were consulted to provide a variety of perspectives on the topics. Only pertinent articles written after 1983 were used in order to maintain the accuracy and timeliness of the material.

Information obtained from the research was condensed into short (6 to 11 page) essays which stress the biological aspects of the topic. Materials with varying degrees of technical difficulty were chosen so that students of all scientific backgrounds could use the bibliography included with each essay for further research. Technical terms were avoided in the development of the essays unless deemed absolutely necessary for understanding and accuracy. Tables and diagrams were included to aid the student in interpreting the written text.

Educational objectives were developed for each essay to assist the student in identifying the significant ideas. The objectives were prepared in accordance with the first three

classifications of cognitive performances (knowledge, comprehension and application) described in Bloom's Taxonomy of Educational Objectives (Bloom *et al.* 1956). Educational objectives belonging to the knowledge category require the recall of specific facts, processes or structures. Comprehension objectives involve an understanding of what is being communicated and its use in specific instances. Objectives dealing with application require the recall and use of generalized ideas or theories in unfamiliar situations. Educational objectives were limited to these classifications because of the difficulty of developing unbiased evaluation material for the remaining three categories of educational objectives dealing with cognitive thinking.

In addition, each essay also contained some discussion of the societal implications of the topic. A supplementary three-page essay entitled "Ethical Implications of Cancer" was developed to provide further statistical and informative material on cancer and carcinogens for the unit on the molecular basis of cancer. A series of four to six personalized questions concerning the ethical issues raised by the essays on the molecular basis of cancer and human gene therapy was provided in order to sensitize the student to the controversies that have arisen or may arise due to the development of human genetic technologies. Questions were personalized in order to help students to become aware of their own moral and ethical stances on these issues.

## **TEACHING METHODS**

Materials for each unit were presented in a systematic manner. On the first day of the unit, students were given a brief, verbal description of the nature of the research. The necessity of student input in the development of the material was stressed. The class instructor informed the

students that participation in any of the activities associated with the research was voluntary, but highly desirable. In order to motivate students to participate in the research activities, students were rewarded with one point extra-credit for each activity in which they took part. Participation in all activities gained the students extra-credit points equivalent to three percent of the total points possible for the class.

In addition to listening to the short introduction the first day of the unit, students were asked to take a twenty question multiple choice pretest. Students were given ample time to complete the pretest. Few students, however, required more than twenty minutes. After collection of the test, packets containing the unit instructional objectives, the essay to be evaluated, a bibliography, tables and diagrams, and any supplementary material were distributed to the students. Students were given approximately one week to read the material.

On approximately the seventh day of the unit, the students received a short lecture (fifteen to thirty minutes in length) explaining the significant points of the essay. Visual aids in the form of overhead transparencies were used to help focus the students' attention. All information presented during the lecture was derived from the essay given to the students earlier in the unit. Students were encouraged to ask questions in order to clarify any ambiguous or vague statements made in the essay or by the lecturer.

Within the next week, students participated in a small group discussion over the essay material. Small group discussions, as described by Hendrix *et al.* (1983), allow students "to identify and clarify:

1. the data from several disciplines that pertain to a specific issue
2. value stances held by the student's peers relative to the issue

3. alternative 'solutions' to the issue and

4. the few 'solutions' that our society might find morally and ethically acceptable."

In addition, small group discussions serve to illustrate and reinforce the course materials (Weaver and Cotrell 1986). Students can "assimilate their readings by sharing their experiences" (Weaver 1983). In the process of formulating their moral and ethical stances, students are required to reflect upon the biological knowledge which may have an influence on their choices. In the non-threatening atmosphere of a well-run group discussion, students with a firmer grasp of the biological bases of the issue can help clarify important biological theories for the other students. Weaver (1983) suggests that students talk more often and more freely in a group setting which allows them to inquire, observe, interpret and learn with their peers.

To ensure that each discussion group provided these benefits for the student, student discussion leaders were chosen in advance of the discussion based upon their past performances on the weekly quizzes and their willingness to serve as leaders. Discussion leaders were provided with a packet (see appendix, pp. XX-XXIV) containing (1) an introduction to successful group discussion leading (Hendrix *et al.* 1983), (2) an attendance sheet, (3) additional discussion questions, and (4) student evaluation forms. The purpose of the packet is to (1) aid the discussion leader in directing the discussion, (2) provide additional material for discussion by expanding upon the personalized ethical questions given to the student on the first day of the unit, and (3) raise ethical issues related to the essay topic but not specifically mentioned in the essay (Hendrix *et al.* 1983).

Students were either assigned randomly to a discussion group or they were allowed to choose their own group. All groups contained fewer than ten participants, including the discussion



leader. Students who took part in the small group discussion over the molecular basis of cancer were asked to complete a personal risk assessment sheet (see appendix, p. XIX) prior to their discussion group meeting. After a forty-minute discussion on carcinogens and their relationship to oncogenes, students were asked to complete a second personal risk assessment sheet and to note if there was any change in their willingness to use substances which may promote cancer. Students participating in the discussion on the potential use of human gene therapy were allowed twenty minutes for discussion. At the end of both of the discussions, students were asked to complete a ten question descriptive evaluation on the value of the essay, the supplementary material, the small group discussion and the unit as a whole. Finally, to conclude the unit, students were asked to take a twenty question multiple choice post-test one week after the small group discussion.

The presentation of the unit on prenatal diagnosis (see appendix, pp. L-LXVII) differed significantly from the presentation of the other two units. The unit on prenatal diagnosis was presented to students for the first time in the spring of 1987 and was, therefore, in a developmental stage. Students were given the essay entitled "Prenatal Diagnosis" and asked to read it within one week. No pretest or lecture was given over the material. All information in the essay was discussed briefly in the regular class lectures, however, allowing the students to pose questions about ambiguous or vague statements. Students were asked to take a twenty question multiple choice post-test to complete the unit. In addition, students were asked to complete a ten question descriptive evaluation which was later used to revise the essay. Educational objectives were developed for the unit, but time constraints prevented their use in this study.

## EVALUATION

Evaluation of the material was performed using two pre-experimental designs. A one-group pretest/post-test format was used to evaluate the units on the molecular basis of cancer and human gene therapy. In this procedure, a pretest is administered prior to the experimental variable to be measured, in this case the essays on the molecular basis of cancer and human gene therapy. After the students have been exposed to the material to be evaluated, a post-test is given. This procedure may be symbolized by the method of Campbell and Stanely (1963) as:

$$O_1 \text{ X } O_2$$

where "X" represents the experimental variable, "O" represents the process of evaluation, and the horizontal sequence represents the same sample of participants performing the procedure in a specific order. It is assumed that the difference between the mean scores of the pretest and post-test is the result of the impact of the experimental material on the students.

A second pre-experimental design was used to evaluate the unit on prenatal diagnosis. In the one-group post-test only format, students are first exposed to the experimental variable to be measured. They are then given a post-test as symbolized in the manner of Campbell and Stanely (1963) as:

$$\text{X } O_1.$$

Any benefits of the experimental material are assumed to be reflected in the students' performances on the post-test.

Pre-experimental research designs, in general, provide little or no control over extraneous

variables (Koul 1986). Because there is no control group in either the one-group pretest/post-test format or the one-group post-test only format, several variables which may affect the outcome of the experiment may not be eliminated. In many studies, the presence of uncontrolled variables prevents the assumption that the difference between the pretest and post-test means is the result of the experimental material exclusively (Koul 1986).

The validity of the study results may be jeopardized by the use of a pretest without a control group. Several researchers suggest that the interaction of the students with the pretest material sensitizes the students to the most significant ideas of the instructional unit. Increased awareness of the students to the test material may precipitate changes resulting in more proficient test-taking by the students (Best 1981). Some investigators suggest the student may remember, even after only brief contact with the pretest material, many of the test questions (Best 1981; Cohen and Manion 1980). It is then possible for the student to "learn" only the specific material covered by the test questions. In ignoring the untested material, the student alters and limits the value of the exercise.

To mitigate the effects of the variable described above on the study results, several steps were taken. The pretest was administered to the students two weeks prior to the post-test. It was thought that the time lapse would reduce any of the residual effects of the pretest. In addition, the questions on the pretest were reordered when constructing the post-test to prevent students from completing the test using a memorized list of answers from the pretest. These measures appeared to be sufficient as evidenced by the small number of students who received lower scores on the post-test than on the pretest.

Maturation of the student and out-of-class experiences may also threaten the validity of the

experimental results (Koul 1986). Long-term studies have shown that students may occasionally do better on the post-test than on the pretest even without experiencing the material to be evaluated. This effect, which is usually found in young children, results from the child's increased ability to think logically and the child's increased range of experiences. The increase in thinking skills and the wider range of experiences may enhance the student's understanding of the topic without the benefit of the experimental material.

In this study, student maturation and out-of-class experiences did not appear to have a significant effect. Students enrolled in Biology 199 are Honors College students who, in general, have obtained a stable level of maturity. It seems unlikely that these students would experience an extraordinary amount of maturation during the two-week-long unit that would invalidate the results of the study. The specific biological nature of the topics discussed limited the possibility that out-of-class experiences would have any effect on the students' understanding of the subject. The absence of biology majors in the study sample makes it possible to assume that none of the students were receiving additional, in-depth instruction in the topics under investigation.

Researchers have also suggested that prior knowledge by the experimenter of the subjects' normal performances could alter the evaluation of the study results (Best 1981). To minimize this problem, all testing materials relied upon objective questions. Pretests and post-tests were graded using computer scanning techniques. Even the descriptive evaluations completed at the end of each unit were constructed in such a manner as to allow the students to answer objectively if they preferred to do so.

Loss of research subjects also presents a problem in the use of pre-experimental research

designs. The effectiveness of teaching material cannot be accurately demonstrated if the student does not participate in both the pretest and post-test, read the material or become involved in the small group discussions. In an attempt to limit errors in interpretation introduced by this source, students who did not participate in all activities in a unit were eliminated from the study sample for the unit.

Pre-experimental designs are particularly sensitive to variables inherent in the use of human subjects. Because there is no control group, the influence of the environment and the time that the test was taken on the study results cannot be ascertained. In addition, such characteristics as motivation and diligence are not only variable between different individuals but also variable within the same person at different times. Reading ability and previous science education may also have some effect on the study results. These factors are significant because the research itself may bring about changes in the students uncharacteristic of their normal behavior which may, in turn, invalidate the study results.

Pre-experimental research is an integral component of action research (Borg 1981). According to Cohen and Manion (1980) action research is the "small-scale intervention in the functioning of the real world and a close examination of such intervention." Action research is applicable to data that are subject to continuous change due to the inconsistent and unpredictable nature of the research subjects (Longstreet 1982). Its use is appropriate in situations in which there is an ongoing need to act and such action cannot be postponed until research is completed.

Action research is particularly effective in the field of education. Borg (1981) suggests that action research "although less rigorous and easier to do than regular educational research...

provides the best approach we know for making educational decisions." "Education is neither an art nor a science," states Longstreet (1982), so it is fitting that the research designs of these areas be blended into a design which is concerned with short-term, tentative generalizations which can be used to direct the development of courses and curricula. It recognizes the fact that decisions must be made in specific, educational situations as an ongoing process for which all data may not be complete. The goal of action research in education is to gather evidence to aid the educator in making decisions which affect everyday classroom procedures (Borg 1981).

## *RESULTS AND DISCUSSION*

### **THE MOLECULAR BASIS OF CANCER**

The first instructional essay entitled "Oncogenes and Cancer" was presented to Biology 199 students in October 1986, six weeks into the fall quarter of the 1986-1987 academic year. Materials were presented in the manner described earlier except that a pretest/post-test evaluation was not used and students were asked to complete only one personal risk assessment sheet. Student reaction to the material was gauged using a ten-question, anonymous, descriptive evaluation.

From this questionnaire and observation of the small group discussions, several conclusions may be made. In general, the unit on oncogenes and cancer served its purpose of sensitizing the students to the possible functions of oncogenes in promoting cancer and to the potential carcinogenic risk of many commonly occurring substances. Ninety-two percent of the students indicated that the discussion on the ethical issues created by the identification of cellular proto-oncogenes and carcinogens was a profitable use of their time (see Table 1, p. 20). The majority of students (88%) also felt that the reading material (essay) provided sufficient information to discuss the questions intelligently. Many students indicated with personal statements that they found the presentation to be informative and enjoyable even though they felt powerless to provide solutions for the ethical problems raised.

Although student evaluations were highly favorable, observation of the small group discussions suggested that some changes were desirable. The essay "Oncogenes and Cancer" was reviewed by a faculty member with extensive knowledge in the areas of virology, immunology, and oncology. With her help, extensive revisions in the essay were made to clarify several points and to enhance the readability of the essay. The name of the essay was also changed to the

TABLE 1.

**RESULTS OF THE DESCRIPTIVE EVALUATIONS OF THE UNIT,  
THE MOLECULAR BASIS OF CANCER  
(DATA IN PERCENTAGES)**

	<b>FALL 1986</b>			<b>SPRING 1987</b>		
	<i>YES</i>	<i>NO</i>	<i>UNDECIDED</i>	<i>YES</i>	<i>NO</i>	<i>UNDECIDED</i>
Did you feel that the discussion moved satisfactorily towards a solution to the problem?	78	20	2 <sup>+</sup>	68	26	6 <sup>+</sup>
Did the discussion cause you to look at the problem from a viewpoint other than your own?	96	6		88	6	6
Did the discussion help you form an opinion on the issue?	86	14		61	10	29
Did the reading material provide you with enough information to discuss intelligently the use of potential carcinogens and the effect that they may have on the human body?	88	12		32	52	16
Do you feel that the discussion was a profitable use of your time?	92	4	4	45	6	49

+ For this question only, the third answer read: "A solution was reached, but not through a logical process."



more inclusive "The Molecular Basis of Cancer" (see appendix, pp. VI–XIV).

Additional changes were made to the supplementary material. Questions concerning the ethical implications of cancer (see appendix, "Ethical Implications of Cancer", pp. XV–XVII) were modified to stimulate greater discussion among the students. The number and range of the questions were reduced as suggested by a couple of students. The actual scope of each question was enlarged, however, to allow the students more freedom and creativity in their discussions. The changes in the discussion questions necessitated a complete revision of the material provided to discussion leaders (see appendix, p. XXII–XXIII) to include more thought-provoking questions.

Slight alterations were made in the personal risk assessment sheet (see appendix, p. XIX) and the descriptive evaluation (see appendix, p. XXIV). A number of qualified "yes" or "no" answers made it reasonable to assume that an "undecided" or "maybe" column was needed in addition to the "yes"/"no" columns. This assumption proved to be justified as most students felt "undecided" about at least one issue on the evaluation and all participants selected at least one "maybe" answer on the personal risk assessment sheet when the unit was presented again in the spring quarter.

When the revised material was presented in the spring quarter, students were asked to take a pretest and post-test (see appendix, pp. I–IV and XXV–XXVII) over the essay material. Educational objectives (see appendix, p. V) were given to the students after the pretest to assist them in preparing for the post-test. Students were also asked to complete a personal risk assessment sheet before and after the small group discussion in order to promote reflection upon the topic.

Several trends were noted upon return of the descriptive evaluations. Only forty-five

percent of the students participating in the small group discussion on the ethical implications of cancer felt that it was a profitable use of their time (see Table 1, p. 20). Another forty-eight percent of the students were undecided as to how worthwhile the discussion was. Sixty-one percent of the students indicated, however, that the discussion helped them to form an opinion on the issue.

Examination of these almost completely conflicting data suggests that several significant factors were influencing the students during the evaluation of the material. The most salient factor may be that the small group discussions on the molecular basis of cancer were conducted outside of class. Students, it appears, have a much more favorable opinion of discussions held during classtime than those held outside of class. It is, therefore, possible that the goals of the discussion were achieved, although the students did not approve of the time at which the discussions were held. This would explain how the majority (68%) of the students could feel that a solution was reached even though they did not feel that the discussion was a profitable use of their time.

In addition, the quality of the discussions may have suffered. Students were conducting their first small group discussion with the presentation of this unit. The supervision normally present in discussions conducted in class was lacking, making it impossible to redirect errant discussions. This lead students to examine only superficially many of the topics raised by the issues and to conclude only that cancer-promoting substances are undesirable. Such conclusions prompted several students involved in one discussion group to suggest that a more controversial subject be selected. It is strongly suspected that these students did not discuss fully the implications of banning suspected carcinogens or of regulating the involuntary use of

carcinogens. Students also took it upon themselves to change discussion groups, causing some students to comment on the ineffectiveness of extremely large or small discussion groups.

The reaction to the reading material was mixed. Thirty-two percent of the students participating in the evaluation of this unit felt that the reading material provided adequate information to discuss intelligently the ethical issues raised by this topic. Fifty-two percent of the students, however, were undecided about the value of the reading material. The majority of the students providing personal comments cited the length of the essay (nine pages) and the use of technical terms as their reasons for indecision about the value of the reading material. The reluctance of the students to strive towards comprehension of the material may be related to a lack of motivation to perform, since the students knew that all participation in the research was voluntary.

Regardless of the results of the descriptive evaluation, a significant amount of learning was shown to have taken place. Students correctly answered an average of 1.54 more questions on the post-test than on the pretest (see Table 2, p. 24). This gain proved to be statistically significant at the 95% level ( $p = 0.025$ ) using a two-tailed  $t$  test. The mean increase in test scores, although statistically significant, was not as high as expected, but can easily be rationalized on the basis of the the voluntary nature of the students' participation in the research.

## **HUMAN GENE THERAPY**

An instructional unit on human gene therapy was developed at the beginning of the winter

TABLE 2.

**EVALUATION OF PRETEST/POST-TEST SCORES FOR  
THREE UNITS OF INSTRUCTION**

UNIT	NUMBER IN SAMPLE	PRETEST MEAN	POST-TEST MEAN	MEAN GAIN	t-test
The Molecular Basis of Cancer (Spring '87)	41	8.49	10.02	+1.54	2.35*
Human Gene Therapy (Winter '86/'87)	72	9.36	12.64	+3.28	7.81**
Human Gene Therapy (Spring '87)	42	8.21	10.90	+2.71	7.52**
Prenatal Diagnosis (Spring '87)	31	—	12.23	—	—

\* Statistically significant at the 95% level ( $p = 0.025$ )

\*\* Statistically significant at the 99% level ( $p = 0.005$ )

quarter of the 1986-1987 academic year. The unit was presented to Biology 199 students during the sixth week of the winter quarter. During the course of the unit, students received all material, including a pretest and post-test, as described earlier.

The descriptive evaluations proved to be generally favorable. Ninety-nine percent of the students felt that the in-class discussion on the ethical issues raised by the potential applications of human gene therapy was a profitable use of their time (see Table 3, p. 26). An overwhelming majority of students (95%) also felt that the discussion helped them to look at the problem from a viewpoint different from their own. Eighty-eight percent of the students were able to develop or reaffirm their opinions on the appropriate use of human gene therapy.

Students who responded with personal comments on the descriptive evaluation were most critical of the essay on human gene therapy (see appendix, pp. XXXIII-XLII). Many students suggested that additional information on the potential risks and consequences of human gene therapy be given. During the discussions, it was observed that students became frustrated when no easily applied solution to a problem was immediately recognizable. The large number of students (42%) dissatisfied with or undecided about the value of the essay may stem from the desire of the students to have the possible risks and consequences of human gene therapy presented to them. Since the presentation of such information by the instructor would defeat the goals of developing critical thinking and creativity established at the beginning of this project, the suggestions of the students were ignored in this particular situation.

Numerous revisions, however, were made in the pretest (see appendix, pp. XXVIII-XXXI). Item analysis of the pretest results showed that several questions were easily answered correctly by the majority of students prior to exposure to the essay on human gene therapy.

TABLE 3.

**RESULTS OF THE DESCRIPTIVE EVALUATIONS OF THE UNIT,  
HUMAN GENE THERAPY  
(DATA IN PERCENTAGES)**

	<b>WINTER 1986-1987</b>			<b>SPRING 1987</b>		
	<i>YES</i>	<i>NO</i>	<i>UNDECIDED</i>	<i>YES</i>	<i>NO</i>	<i>UNDECIDED</i>
Did you feel that the discussion moved satisfactorily towards a solution to the problem?	60	29	6 <sup>+</sup> *	69	27	4 <sup>+</sup>
Did the discussion cause you to look at the problem from a viewpoint other than your own?	95	5		88	10	2
Did the discussion help you form an opinion on the issue?	59	10	29 <sup>**</sup>	61	16	20 <sup>**</sup>
Did the reading material provide you with enough information to discuss intelligently the potential use of human gene therapy?	58	16	26	51	6	43
Do you feel that the discussion was a profitable use of your time?	99	1		78	8	12 <sup>*</sup>

+ For this question only, the third answer read: "A solution was reached, but not through a logical process."

\* Some rows do not total 100% due to omitted or unique answers by the students.

\*\* For this question only, the third answer read: "I already had an opinion."

Review of the test by a faculty member with expertise in the area of education suggested that a few questions did not measure the information underlying the educational objectives (see appendix, p. XXXII) given to the students before the pretest. Several questions were, therefore, deleted from the pretest and replaced with similar but better-worded questions in order to increase the clarity and, in some cases, the difficulty of the questions.

The change in questions destroyed the possibility of making a statistically valuable comparison between the pretest and post-test scores. In this case, however, a two-tailed  $t$  test was performed on the data to provide some indication of the students' level of achievement in this unit. Students averaged 3.28 more correct answers on the post-test than on the pretest (see Table 2, p. 24). This increase proved significant at the 99% level ( $p = 0.005$ ) suggesting that the essay and the group discussion did have an effect on the students' understanding of the procedures and potential uses of human gene therapy.

Based upon the descriptive evaluations, the pretest/post-test results and the strong positive feedback from the students, the unit on gene therapy received no additional changes before presentation to Biology 199 students in the spring quarter of the 1986-1987 academic year. Descriptive evaluation again showed that the students perceived the unit to be worthwhile (see Table 3, p. 26). Seventy-seven percent of the students felt that the in-class discussion was a profitable use of their time. The discussion caused eighty-eight percent of the students to look at the problems associated with the use of human gene therapy from a viewpoint different from their own and helped sixty-one percent of the students to form an opinion on the issues.

Pretest and post-test results were compared using a two-tailed  $t$  test (see Table 2, p. 24). Results of the  $t$  test indicated that the students showed a highly significant ( $p = 0.005$ )

increase in their post-test scores. Each student answered approximately 2.71 more questions correctly on the post-test than on the pretest.

### **PRENATAL DIAGNOSIS**

An essay on the recent advances in prenatal diagnosis (see appendix, pp. LI-LXII) was presented to students during the third week of the spring quarter. The material was presented in the manner described earlier. Descriptive evaluations were completed after the post-test was administered. Students were strongly encouraged to make suggestions which would improve the value of the essay to the students.

Overall, the descriptive evaluations indicated that the essay was a valuable addition to the course content (see Table 4, p. 29). Ninety percent of the students who read the essay found it to be interesting. The majority of students felt that the essay was not only easy to understand itself, but that it also increased their understanding of the lecture material. This was particularly significant since ninety-seven percent of the students indicated that the essay presented new material to them.

In addition, several of the students responded with personal comments. One student suggested that subheadings be inserted in the essay to make it easier to find specific information within the essay. Another student indicated that the abbreviation "NTDs" was never explained in the essay. A very few students commented on what they perceived to be the difficult nature of the language, while other students suggested that the simplicity of the language may insult the students'



TABLE 4.

**RESULTS OF THE DESCRIPTIVE EVALUATIONS OF THE UNIT,  
PRENATAL DIAGNOSIS  
(DATA IN PERCENTAGES)**

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	<b>SPRING 1987</b>		
	<i>YES</i>	<i>NO</i>	<i>UNDECIDED</i>
<hr/>			
Was the reading material interesting?	90		10
Was the reading material easy to understand?	87	5	8
Did the reading material assist you in your understanding of the lecture?	77	5	18
Do you feel that the handout was a valuable addition to the lecture?	82	5	13
Did the handout present new information to you?	97	3	

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intelligence. Suggestions made by the students were reviewed and appropriate revisions were made in the essay.

A post-test (see appendix, pp. LXIII-LXVI) was administered at the end of the unit to provide an additional measure of the effectiveness of the essay. Students correctly answered an average of 12.23 questions on the post-test (see Table 2, p. 24). This mean score compares favorably with the mean scores of this sample of students on other post-tests and is, in fact, higher than all other post-test scores. Although it cannot be assumed that the mean score reflects exclusively the impact of the essay on the students, the essay can, at least, be considered a contributing factor to the post-test scores.

Based upon the preliminary data described above, the unit on prenatal diagnosis could well be expanded to include activities similar to those used in the study of the molecular basis of cancer and human gene therapy. Students seem particularly interested in the recent advances made in prenatal diagnosis because of its growing prevalence in American society. In the fall quarter of the 1987-1988 academic year, Biology 199 students, in addition to participating in all previously developed activities, may be asked to complete a pretest and to participate in a small group discussion treating the uses of prenatal diagnosis. The information gained from the use of a pretest/post-test format and a second set of descriptive evaluations would be used to provide a more accurate evaluation of the effectiveness of the essay and discussion as teaching tools. If the material is found to be effective, it will be incorporated into the course content with the units on the molecular basis of cancer and human gene therapy.

## *SUMMARY*

Human genetics is a rapidly growing field. Its phenomenal growth has necessitated the constant revision of college course content in the area of human genetics in order to ensure that students receive accurate, up-to-date information on some of the most revolutionary research being performed today. In this study, three topics — the molecular basis of cancer, human gene therapy, and prenatal diagnosis — were chosen for development and incorporation into an Honors College symposium in human genetics (Biology 199) at Ball State University in Muncie, Indiana.

Instructional units covering each topic were constructed for presentation to Biology 199 students during the 1986–1987 academic year. Each unit revolved around the information presented in a short essay on the topic. Students received a lecture and/or participated in a small group discussion treating the material. The effectiveness of the essay and the discussion groups as teaching tools was evaluated using pretests, post-tests, and descriptive questionnaires.

From the evaluation of the material, it appears as if all three units were successful in increasing the students' awareness of the rapid advances being made in the field of human genetics. The majority of students felt, as indicated by the descriptive evaluations, that the small group discussions were a profitable use of their time. In addition, many of the students were able to develop opinions about the ethical issues raised by these topics. Students also showed a statistically significant increase in test scores after reading the essays and participating in small group discussions treating the molecular basis of cancer and human gene therapy.

In a world characterized by continuous change, the educator's task is often a difficult one. The

future is rarely predictable and society is subject to a variety of pressures and influences. It is the educator's task to help students learn to cope with this situation. Through the presentation of the three instructional units developed during this study, it is hoped that students gained some appreciation of the need for scientific literacy in an increasingly scientific world. By simply being aware of the biological facts and the societal implications of these facts, students ought to be in a better position to cope with either personal or societal problems in the field of human genetics when they arise. Whether the larger goal of the instructional units developed in this study — the preparation of the students in some small way for the future — has been achieved, will only be known to the individual students should they confront human genetics problems later in life.

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## THE MOLECULAR BASIS OF CANCER QUIZ

1. The activation of a proto-oncogene to a state which may promote cancer is thought to be
  - a. a single, irreversible step.
  - b. a single, reversible step.
  - c. a multistep process.
  - d. a completely unknown mechanism.
2. Oncogenes carried by retroviruses are thought to be
  - a. unique viral genes which developed by mutation during evolution.
  - b. unique viral proteins which have been highly conserved during evolution.
  - c. altered pseudo-oncogenes acquired from some previous infection of the host cell's genome.
  - d. altered proto-oncogenes acquired from some previous infection of the host cell's genome.
3. Before both retroviruses and DNA viruses can have any cancer-inducing effect on a cell, they must
  - a. insert their genetic material into the host cell's DNA.
  - b. insert their proteins into the host cell's DNA.
  - c. produce numerous viral proteins using the host cell's ribosomes.
  - d. produce numerous progeny identical to themselves.
4. Amplification is thought to cause cancer by the increased production of proteins which
  - a. inhibit the effects of growth inhibiting factors.
  - b. cause the cells to destroy themselves.
  - c. enhance the cell's ability to resist drugs.
  - d. enhance the cell's ability to survive radiation treatments.
5. In cases where amplification does not appear until after diagnosis of cancer, amplification appears to be strongly related to
  - a. tumor regression.
  - b. tumor progression.
  - c. patient recovery.
  - d. patient death.
6. Proto-oncogenes often affected by mutations promoting cancer, are genes for
  - a. structural components of bone cells.
  - b. oxygen-carrying molecules of the blood.
  - c. growth factors and their receptors.
  - d. pigment in the skin cells.





13. Individuals who inherit the deletion of one Rb gene (for retinoblastoma) are likely to develop tumors in both eyes because the production of cancer may require only
- a. a chromosome translocation.
  - b. the activation of a proto-oncogene.
  - ☒ c. the inactivation of the second Rb gene.
  - d. the infection of the cell by a virus.
14. Insertional mutagenesis involves
- ☒ a. placing one of the host's genes under the control of a viral promoter.
  - b. destabilizing the virus' chromosomes and thereby promoting chromosome breakage.
  - c. placing one of the virus' genes under the control of the host's promoter.
  - d. separating a viral gene and its promoter.
15. Enhancers increase the rate of
- a. transfection of nearby genes.
  - b. translocation of distant genes.
  - c. translation of distant genes.
  - ☒ d. transcription of nearby genes.
16. Retroviruses containing oncogenes infect normal cells and produce a malignant phenotype in a process known as
- a. viral mutagenesis.
  - b. viral translation.
  - ☒ c. viral transduction.
  - d. viral insertion.
17. According to the somatic mutation hypothesis, all of the following may explain how oncogenic changes occur EXCEPT
- a. viruses.
  - ☒ b. present medical practices.
  - c. chemicals and radiation.
  - d. spontaneous mutations.
18. Activated oncogenes and DNA damage have been found in
- a. all of the cells of all of the cancers studied.
  - b. none of the cells of any of the cancers studied.
  - c. some of the cells of all of the carriers studied.
  - ☒ d. some of the cells of only some of the cancers studied.
19. Interest in proto-oncogenes, oncogenes and antioncogenes is increasing because
- a. they are easily discovered.
  - b. they are present in all cells of all animals.
  - ☒ c. they may provide useful information for the future prevention, diagnosis, and treatment of cancer.
  - d. they are presently known to be responsible for all forms of cancer which afflict man.

20. Genetically inherited abnormalities may predispose a cell to cancer by

- a. increasing the cell size.
- ⓑ. lessening the number of steps necessary to produce cancer.
- c. eliminating the cell from the body.
- d. increasing the length of time needed for each mutation leading to cancer to occur.

OBJECTIVES FOR THE  
MOLECULAR BASIS OF CANCER

1. Distinguish between oncogene, proto-oncogene, and antioncogene.
2. Compare how retroviruses and DNA viruses may promote cancer.
3. Describe the role amplification may play in promoting cancer.
4. Explain how several mutations may promote cancer.
5. Describe how a structural change in a gene due to a chromosomal translocation may cause cancer.
6. Describe how a regulatory change in a gene due to a chromosomal translocation may cause cancer.
7. Explain how antioncogenes may suppress or promote cancer.
8. Define such terms as retrovirus, amplification, fragile site, enhancer, insertional mutagenesis, and viral transduction.
9. Outline the somatic mutation hypothesis of cancer induction.
10. Identify some of the problems associated with the theory of oncogenes.

## THE MOLECULAR BASIS OF CANCER

Cancer, or malignant tumors, are made up of a large number of uncontrollably replicating cells which have all arisen as daughter cells of one malignantly transformed parent cell. At present, scientists are of the opinion that this malignant parent cell probably comes into being as a result of a multistep process. During this process, genetic alterations progressively accumulate until eventually the previously normal cell is transformed into a cell which reproduces itself without constraint and often spreads throughout the body. In recent years, work has shown that this transformation process may include the activation of oncogenes (onco = cancer) or the inactivation of anti-oncogenes. ONCOGENES are genes that have the capacity to contribute to the development of a cancerous cell from a normal cell. They are apparently derived from PROTO-ONCOGENES which are normal cellular genes that become oncogenes through structural or regulatory changes. Of the estimated 50,000 genes thought to exist in the human genome, fewer than 100 are thought to be proto-oncogenes. To date, thirty-plus proto-oncogenes have been identified. It is assumed that proto-oncogenes provide essential functions for the cell, since they have been highly conserved. Conserved genes are those genes which have evolved through the centuries within many species with few, if any, changes. ANTIONCOGENES, or suppressor genes, inhibit the formation of tumors by preventing or modifying the expression of oncogenes. Tumors may form when the suppressor gene is inactivated by mutation or deletion.

The somatic mutation hypothesis has been developed to explain how

cancer-causing or oncogenic changes may occur. Some cancers, the hypothesis suggests, result from spontaneous mutations. They represent a "background" level of cancer which, presumably, society will always have. Other cancers may be initiated by viruses or environmental agents such as chemicals or radiation which induce mutations, deletions or rearrangements in a cell's chromosomes. Genetically inherited abnormalities may predispose a cell to cancer by lessening the number of steps necessary to produce cancer. These changes in the genetic make-up of a cell are thought to affect the DNA of proto-oncogenes or antioncogenes in such a way that their activity or inactivity leads to a cancer. Although the evidence cannot yet be considered as proof, clinical data as well as results of many experiments appear to support these views.

#### VIRUSES AND CANCER

Two types of viruses may influence the formation of cancer. Some RETROVIRUSES, which are capable of converting their genomic RNA into DNA and inserting it into the host's DNA, contain the first identified oncogenes. When viruses containing these oncogenes infect normal cells, these cells may become transformed to a malignant phenotype. This process is called "viral transduction." These oncogenes are thought to be altered proto-oncogenes acquired from some previous host cell's genome, during an earlier infection. In order to avoid confusion, scientists symbolize proto-oncogenes and oncogenes with the prefix v for virus or c for cell and three letters taken from the name of the tumor from which the oncogene was first isolated. For example, v-sis is a viral oncogene first discovered in a simian sarcoma; c-sis is the cellular proto-oncogene counterpart of the v-sis gene.

DNA viruses are also capable of inserting their DNA into the host's genome. Some of these viruses, such as the human papilloma virus, are thought to contain cancer-causing genes unique to the virus. Other DNA viruses, as well as some retroviruses, which do not contain known cancer-causing genes may produce cancer by 1) inactivating one of the host's genes or its regulatory mechanism, 2) separating a gene and its promoter, 3) placing one of the host's genes under the control of a viral promoter, or 4) destabilizing the host's chromosomes thereby promoting chromosome breakage. This kind of cancer-promoting damage is called "insertional mutagenesis."

#### ONCOGENES AND CANCER

AMPLIFICATION of proto-oncogenes occurs when replication of the gene is increased so that several copies of it are present in the cell's genome. Increased numbers of the gene may result in the increased production of the gene product. The large amount of gene product may play a role in tumor progression by limiting the effects of growth inhibiting factors on a cell, thereby preventing terminal differentiation. One example of amplification is neuroblastoma in which 3 to 300 copies of the gene N-myc, a variant of c-myc, may exist in a cancerous cell. In 95% of the patients with early forms of neuroblastoma there was little or no amplification, while in half the patients with advanced forms of neuroblastoma at least ten or more copies of the gene were present. Since in some cases amplification did not appear until after the diagnosis of neuroblastoma, amplification may be an effect rather than a cause of the cancer. In any event, amplification seems to correlate well with tumor progression.

Mutations, either spontaneous or induced, may lead to the

activation of a proto-oncogene, changing it from a normal cellular gene into an oncogene. One group of proto-oncogenes which may be affected by mutations are those genes that control cell division by coding for growth factors or their receptors. Mutations in these genes can significantly alter the growth pattern of cells. In one experimental system, the replacement of guanine by thymine at one location in the 5,000 nucleotides of the c-ras proto-oncogene causes a precancerous cell to become cancerous. The normal protein coded for by the c-ras gene is bound to the cell membrane and functions as a carrier of signals from membrane-bound receptors. In its capacity as a carrier, the protein binds guanosine triphosphate (GTP) and then rapidly converts it to guanosine diphosphate (GDP). In the presence of the mutated form of the c-ras protein, conversion of GTP to GDP is slowed significantly which disturbs the regulation of cell growth.

As another example, mutations in the c-erb-B gene cause the growth factor receptors on the cell membrane to be deformed. A mutated c-erb-B gene produces a truncated form of the epidermal growth factor receptor. The protein produced loses binding specificity for the epidermal growth factor, but it retains its ability to add phosphate to the amino acid tyrosine which may function as a stimulus for cell division. The deformed receptor frees the cell from its dependence on an external growth factor, which allows the cell to grow and divide indefinitely.

The c-sis gene codes for one polypeptide chain of platelet-derived growth factor (PDGF) which triggers wound repair by stimulating the growth of connective tissue around the wound. A mutation in the c-sis gene or the gene which regulates it causes a PDGF-like protein to be secreted from a cell. As these cells also have

receptors for PDGF, they are capable of self-stimulation. This self-stimulating activity is unusual since normal cells do not often produce both a growth factor and receptors for that same growth factor. Thus, a cell with a mutated c-sis gene, which has both functions, may no longer be dependent on neighboring cells to control its growth and, potentially, can grow continuously. Mutations of genes which control transcription may also alter proto-oncogenes causing them to become oncogenes, but little is understood of the mechanism by which they might work.

#### CHROMOSOME TRANSLOCATIONS

Chromosome translocations may also cause the activation of proto-oncogenes by changing the physical setting of the gene. The changes in the gene's physical environment may cause structural or regulatory changes in the proto-oncogene's product. Chronic myelocytic leukemia (CML) is an example of a cancer which is associated with a translocation leading to a structural change in the product of a proto-oncogene. In CML, the c-abl gene on chromosome 9q34 is involved in a reciprocal translocation with a limited segment of chromosome 22 known as the breakpoint cluster region (bcr) which contains the c-sis proto-oncogene. The shortened chromosome 22 formed by the translocation is known as the Philadelphia chromosome and is found in 96% of the individuals having CML. After the translocation, the protein produced by the c-abl gene is altered. One end is lost from the normal protein and replaced by a much longer polypeptide chain that produces an abnormal activity in the protein. This abnormal protein product may increase the cell's ability to proliferate.



Burkitt's lymphoma is an example of a cancer associated with both a viral infection and a chromosomal translocation that may produce a change in the regulatory function of a proto-oncogene. Several predisposing factors seem to be necessary, however, before the proto-oncogene activation occurs. One predisposing factor to Burkitt's lymphoma is the infection of the body by the Epstein-Barr virus (EBV). When infected with EBV, antibody-forming cells of the immune system (B-cells) may become activated and proliferate wildly. The infected cells, which often contain several copies of the viral genes, may grow and divide for a much longer period than would uninfected cells, apparently increasing the risk of translocation. In addition, environmental cofactors may also predispose oncogene activation. In Africa where a high incidence of Burkitt's lymphoma is found, many people suffer from chronic malaria as well as from EBV infection. The large number of parasites in the cell may increase the number of actively dividing B-cells in the blood and may increase the risk that fragile sites on the chromosomes will be destabilized. FRAGILE SITES are points where chromosomes often break giving rise to translocations. In most cases, a reciprocal translocation between 8q24 and 14q32 is associated with the onset of Burkitt's lymphoma. Other translocations involving chromosomes 2 and 8 and chromosomes 8 and 22 have also been associated with the onset of Burkitt's lymphoma. All of these translocations place the c-myc gene from chromosome 8 in the middle of genes which code for portions of immune system molecules. The c-myc gene is thought to help maintain the proliferative state in growing and dividing cells. Apparently during the translocation, the c-myc gene is removed from its normal regulatory region and placed under the control of the B-cell gene enhancers where it seems to

maintain the wildly proliferative state of the cancer cells. **ENHANCERS** are gene loci which increase the rate of transcription of nearby genes. Increased transcription of the c-myc gene seems to prevent the B-cells from differentiating into nondividing memory cells. In terminally differentiated cells and G<sub>0</sub> and G<sub>1</sub> cells, the c-myc gene is not transcribed. The translocation of the c-myc gene may cause it to be transcribed continuously. Since the proteins produced by the c-myc gene in both its normal and translocated positions are qualitatively the same, Burkitt's lymphoma appears to be the result of altered regulation of the c-myc gene.

#### ANTIONCOGENES

Antioncogenes, or suppressor genes, behave in a much different manner than proto-oncogenes. An affected individual must be homozygous for the inactivation in order for tumor formation to occur. This inactivation may result from deletions or mutations.

Retinoblastoma appears to be an example of a cancer associated with the inactivation of an antioncogene. Retinoblastoma, a cancer of the eye, is usually found in children under the age of five. It may be viewed as either the result of: (a) the loss of both alleles of a dominant tumor suppressor gene or (b) a "recessive oncogene" which in the homozygous recessive condition allows the formation of cancer. In either event, the Rb gene on chromosome 13q14 is somehow inactivated, which prevents the terminal differentiation of the cell. The inactivation which allows tumor development apparently occurs in two ways. In hereditary retinoblastoma, one inactive Rb gene may be inherited and the second Rb gene appears to be inactivated, or lost, through mutation, mitotic nondisjunction, or mitotic recombination. In

nonhereditary retinoblastoma, both genes are inactivated through changes in the somatic cells. Since the individual with an inherited inactivation of an Rb gene needs only one additional mutation to produce the homozygous condition, that individual is more likely to develop tumors in both eyes. Individuals who have inherited two active Rb genes must produce two chromosome mutations or deletions in order to have the homozygous condition. The chances of this occurring are much lower, so retinoblastoma tends to occur in only one eye of these individuals. In addition to the inactivation of the antioncogene Rb, positive oncogene influence may also be necessary for tumor development. Amplification of the N-myc gene has been observed in several retinoblastoma cell lines. Other chromosomal aberrations (trisomy 1, 6q deletions, inversions of 6q) have been observed in retinoblastoma cell lines as well. There is evidence to suggest that the Rb gene may suppress other oncogenes besides the one which may cause retinoblastoma, since many individuals who are cured of retinoblastoma later develop primary tumors in other parts of the body.

### Conclusion

Scientists today are a long way from understanding the mechanisms which govern the origin of cancer. Increasing evidence, however, suggests that many cancers may originate from some type of damage to an individual's DNA. This damage may result in mutations, translocations, amplification of proto-oncogenes or the insertion of viral genes into an organism's genome (insertional mutagenesis). Neuroblastoma, for example, is a cancer associated with proto-oncogene amplification. Chronic myelocytic leukemia and Burkitt's lymphoma, on the other hand, are associated with chromosomal translocations. Although DNA damage

has not been found in all cancer-cell types and may never be found in some, the increase in understanding gained by exploring the possible molecular basis of some cancers may provide useful information for the future prevention, diagnosis, and treatment of all cancers.

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